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April 22, 2020

To: Wei Huang, Associate Editor, Science of The Total Environment

Date: April 6, 2020

Re: U.S. Environmental Protection Agency concerns regarding the validity of recently published meconium study

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In Volume 707 of the *Science of The Total Environment* journal, there is a short communication article[1] titled "Meconium identifies high levels of metals in newborns from a mining community in the U.S.", authored by researchers from the University of South Carolina (Drs. McDermott and Lead) and Montana Tech (Dr. Hailer). This article will hereafter be referred to as the McDermott et al. study. The McDermott et al. study collected meconium[2] samples from infants born in Butte, Montana and Columbia, South Carolina. The authors reported that the meconium data from this study demonstrate that *"[t]he high concentrations of metals…for the 15 newborns in Butte are cause for immediate concern. The magnitude of the differences in concentrations in Butte compared to Columbia is 1792-fold higher for Cu, 1650-fold higher for Mn and 1883-fold higher for Zn."* The article concludes with the following statement: *"We believe that there is an urgent need for further research to understand the mechanisms and the human consequences of this potential public health emergency."*

The city of Butte, Montana is located within the Silver Bow Creek/Butte Area Superfund Site. Since 1987, the U.S. Environmental Protection Agency (EPA) has been conducting cleanup activities at the site to address metal contamination, primarily lead and arsenic, resulting from historical mining within this region. In fact, millions of cubic yards of soils have been remediated or removed in Butte. The McDermott et al. study was first published online in late November 2019, and its conclusions generated considerable concern in the Butte community when the local newspaper published the study findings and conducted interviews with the study authors ("Health study shows startling levels of metals in Butte babies' meconium", Montana Standard, November 26, 2019[3]). The public health emergency claims made by the study authors and the fact that the study identified copper, manganese, and zinc as being of potential concern also garnered the attention of the EPA Superfund team and other State and local agencies associated with the site. Copper, manganese, and zinc were evaluated as part of the original

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[1] [HYPERLINK "https://doi.org/10.1016/j.scitotenv.2019.135528"]

[2] Meconium is the first stool passed by a newborn, usually during the first 24 hours after birth.

[3] [HYPERLINK "https://mtstandard.com/news/local/health-study-shows-startling-levels-of-metals-in-butte-babies-meconium/article_d7c10bb3-68b6-588f-9028-a828ab17d034.html"]

baseline human health risk assessment for the Superfund site and were excluded as being contaminants of concern at the site because they did not present a risk to the community.

Over the past few months, EPA has been reviewing the published literature on meconium levels to further evaluate the results of the McDermott et al. study. EPA reviewed 18 published studies, spanning from 1966 to 2019, on metal concentrations in meconium. The attached reference list provides the citation for every meconium study reviewed by EPA (including all meconium studies referenced by the paper). **Table 1** summarizes the meconium results for copper, manganese, and zinc from the McDermott et al. study (shown in grey) and compares these levels to meconium concentrations reported in the scientific literature. Because the McDermott et al. study reported concentrations as wet weight and most other literature reported concentrations as dry weight, this table also presents EPA's conversion of the McDermott et al. study concentrations to dry weight.

Figure 1 presents a graphical illustration of this comparison for copper, manganese, and zinc. In this figure, the green and red lines represent the approximate median concentration (dry weight) for the Butte and Columbia datasets, respectively. As shown, this comparison indicates the meconium concentrations for the Butte dataset are generally consistent with the results in the scientific literature. Inspection of Figure 1 also indicates the meconium concentrations for the Columbia dataset are uncharacteristically low, by nearly three orders of magnitude, compared to the scientific literature. Thus, the McDermott et al. study conclusions that Butte concentrations are "1792-fold higher for Cu, 1650-fold higher for Mn and 1883-fold higher for Zn" are not suggestive of a health issue in Butte but rather biased by the use of an unrepresentative control.

The presence of copper, manganese, and zinc in meconium samples throughout the scientific literature is not unexpected, as these are essential elements and are required in normal maternal diet and are frequently included in prenatal vitamins. Manganese is essential mineral nutrient needed for proper fetal development and other important aspects of metabolism. Copper and zinc are also essential micronutrients that play an essential role in fetal development. Indeed, deficiencies of copper and/or zinc during pregnancy have been linked with adverse outcomes, including abortion, preterm delivery, and stillbirth.

EPA suspected the magnitude of the differences in meconium concentrations in Butte compared to Columbia as reported in the McDermott et al. study might have been a consequence of a unit's error. Thus, EPA contacted the study authors to request the raw laboratory instrument output to verify if there may have been an error in the results reporting. The researcher from Montana Tech (Dr. Hailer) readily provided the instrument output for the Butte samples and EPA was able to confirm the results for Butte reported by the instrument are consistent with the values presented in the article. However, the researchers from University of South Carolina (Drs. McDermott and Lead) have not provided the instrument output for the Columbia samples. Therefore, EPA has not been able to review this dataset, nor have the researchers responded to subsequent EPA requests for additional information and dialog regarding the study results.

EPA has concerns with the validity of the meconium data for the Columbia samples and the authors' conclusions that have been published in your journal. The Agency for Toxic Substances and Disease Registry (ATSDR) has also indicated similar concerns with the McDermott et al. study (see the attached letter from ATSDR to the state and local health departments). Because of the serious and likely erroneous nature of the purported health claims made in this article; we are requesting that the *Science* *of The Total Environment* independently review the scientific merits of this study. If the journal determines the reported meconium results are in error and the study conclusions are not supported, we request that the journal retract the study. We are available to discuss any concerns at your convenience.

Respectfully,

Nikia Greene
EPA, Region 8, Remedial Program Manager

Dr. Charles Partridge
EPA, Region 8, Toxicologist

Attachments:

TABLE 1. SUMMARY OF MECONIUM METAL CONCENTRATIONS PRESENTED IN THE LITERATURE

FIGURE 1. COMPARISON OF MECONIUM METAL CONCENTRATIONS

ATSDR letter "*RE: Butte Meconium Health Study Concerns*", from to Karen Sullivan (Butte-Silver Bow Health Department) Laura Williamson (Montana Department of Health and Human Services) dated December 13, 2019.

Citations of Reviewed Literature:

Arbuckle, TE, Chun Lei Liang, Anne-Sophie Morisset, Mandy Fisher, Hope Weiler, Ciprian Mihai Cirtiu, Melissa Legrand, Karelyn Davis, Adrienne S. Ettinger, William D. Fraser. 2016. Maternal and fetal exposure to cadmium, lead, manganese and mercury: The MIREC study. Chemosphere 163:270-282. DOI: 10.1016/j.chemosphere.2016.08.023 [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0045653516310402"]

Aziz, Sina & Ahmed, Shakil & Karim, Saadiya & Tayyab, Subhana & Shirazi, Anisa. 2017. Toxic metals in maternal blood, cord blood and meconium of newborn infants in Pakistan. Eastern Mediterranean health journal 23:678-687. DOI: 10.26719/2017.23.10.678. [HYPERLINK "https://www.researchgate.net/publication/322024836_Toxic_metals_in_maternal_blood_cord_blood_and_meconium_of_newborn_infants_in_Pakistan"]

Baranowski, J and I Baranowska. 1996. Meconium analysis using AAS for screening the intrauterine exposure to heavy metals in an ecological disaster region. Metal Ions in Biology and Medicine, Volume 4, pp 651-653. Proceedings of the Fourth International Symposium on Metal Ions in Biology and Medicine held in Barcelona (Catalonia), Spain, on May 19-22, 1996. [HYPERLINK "https://books.google.com/books?id=MQ3WneF3PAsC&lpg=PA651&ots=OYXKKduCgo&dq=baranowski%201996%20meconium&pg=PA654" \l "v=onepage&q=baranowski%201996%20meconium&f=false"]

Cassoulet, R, Lounes Haroune, Nadia Abdelouahab, Virginie Gillet, Andrea A. Baccarelli, Hubert Cabana, Larissa Takser, Jean-Philippe Bellenger. 2019. Monitoring of prenatal exposure to organic and inorganic contaminants using meconium from an Eastern Canada cohort. Environmental Research 171:44-51. DOI: 10.1016/j.envres.2018.12.044 [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0013935118306807"]

Ettinger, AS, Tye E. Arbuckle, Mandy Fisher, Chun Lei Liang, Karelyn Davis, Ciprian-Mihai Cirtiu, Patrick Bélanger, Alain LeBlanc, William D. Fraser. 2017. Arsenic levels among pregnant women and newborns in Canada: Results from the Maternal-Infant Research on Environmental Chemicals (MIREC) cohort. Environmental Research 153:8-16. DOI: 10.1016/j.envres.2016.11.008 [HYPERLINK "http://www.sciencedirect.com/science/article/pii/S0013935116304534"]

Friel JK, Matthew JD, Andrews WL, Skinner CT. 1989. Trace elements in meconium from preterm and full-term infants. Biol Neonate. 55(4-5):214-7. DOI: 10.1159/000242919 [HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/2719992"]

Golamco, Florence & Harper, Rita & Sia, Christiane & Spinazzola, Regina & Wapnir, Raul. 2000. Mineral and trace elements in meconium: Comparison in dizygotic twin pairs. Journal of Trace Elements in Experimental Medicine - J Trace Elem Exp Med. 13. 205-213. DOI: 10.1002/(SICI)1520-670X(2000)13:23.0.CO;2-T [HYPERLINK "https://www.researchgate.net/publication/246853361_Mineral_and_trace_elements_in_meconium_Comparison_in_dizygotic_twin_pairs"]

Gonzalez de Dios, Javier & Moya, Manuel & Cortés, Ernesto. 1996. Quantification of fecal excretion of trace elements in newborns as expression of fetal intestinal secretion. Anales españoles de pediatría. 45. 281-5. [HYPERLINK "https://www.researchgate.net/publication/14189316_Quantification_of_fecal_excretion_of_trace_elements_in_newborns_as_expression_of_fetal_intestinal_secretion"]

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Haram-Mourabet S1, Harper RG, Wapnir RA. 1998. Mineral composition of meconium: effect of prematurity. J Am Coll Nutr. 17(4):356-60. DOI: 10.1080/07315724.1998.10718775 [HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/9710845"]

Kopito, L and H Shwachman. 1966. Mineral composition of meconium. The Journal of Pediatrics, Volume 68, Issue 2, 313 – 314. [HYPERLINK "https://www.jpeds.com/article/S0022-3476(66)80166-X/abstract"]

Lall, R and Wapnir, RA. 2005. Meconium mineral content in small for gestational age neonates. Am J Perinatol. 22(5):259-63. DOI: 10.1055/s-2005-870660 [HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/16041636"]

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**Turker G, Ozsoy G, Ozdemir S, Barutçu B, Gökalp AS. 2013. Effect of heavy metals in the meconium on preterm mortality: preliminary study. Pediatr Int. 55(1):30-4. DOI: 10.1111/j.1442-200X.2012.03744.x [HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/23061406"]

Vall O, Gómez-Culebras M, Garcia-Algar O, et al. 2012. Assessment of prenatal exposure to arsenic in Tenerife Island. PLoS One. 7(11):e50463. DOI:10.1371/journal.pone.0050463 [HYPERLINK "https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3508998/"]

Yang Y, Nakai S, Oda S, Nishino H, Ishii M, Yokoyama H, Matsuki H. 2013. A preliminary study on the use of meconium for the assessment of prenatal exposure to heavy metals in Japan. J UOEH. 35(2):129-35. DOI: 10.7888/juoeh.35.129 [HYPERLINK "https://www.ncbi.nlm.nih.gov/pubmed/23774656"]

**In its review of this study, EPA identified a suspected unit error in the meconium results reported for this study. Direct correspondence with the primary study author, Dr. Gulcan Turker, on January 2, 2020, confirmed that results were incorrectly reported in the journal article as ng/g/kg when they should have been reported as μg/g/kg.

TABLE 1. SUMMARY OF MECONIUM METAL CONCENTRATIONS PRESENTED IN THE LITERATURE

Metal	Meconium Concentration (µg/g)									
	McDermott et al. (2019)				Cassoulet et al. 2019*		MIREC (Arbuckle et al. 2016/ Ettinger et al. 2017)*			Aziz et al. 2017
	n=15		*n=17*		*n=371*		*n=1,591*			*n=309*
	Butte, MT Median		Columbia, SC Median		Median	Range	Median	95th %tile	Maximum	Mean Range by Location (dry wt.)
	as wet weight [a]	as dry weight [b]	as wet weight [a]	as dry weight [b]						
Copper	26.311	88	0.01468	0.049	67.18	15 - 250	---	---	---	1.6 - 28.7
Manganese	5.364	18	0.00325	0.011	14.31	1 - 100	4.9	15	40	---
Zinc	81.642	272	0.04334	0.14	313.8	20 - 1,500	---	---	---	9.5 - 160.3

Metal	Meconium Concentration (µg/g) [continued]									
	Hamzaoglu 2014	Turker et al. 2013	Turker et al. 2006	Lall et al. 2005	Golamco et al. 2000	Haram-Mourabet 1998	Gonzalez de Dios 1996	Baranowski 1996	Friel 1989	Kopito 1966
	n=18	*n=304*	*n=117*	*n=15*	*n=26*	*n=34*	*n=38*	*n=26*	*n=27*	*n=65*
	Non-industrial district, Median	Surviving, Median [c]	Median	AGA Newborns, Mean (dry wt.)	Range of means, >36wks (dry wt.)	Mean Range by Gest. Age	Full-term, Mean (Table III)	Control Mean	Mean, full-term [d]	Control Mean
Copper	67.05	99.77	116.8	115.8	79.7 - 93.6	90.3 - 154.2	36.4	15.2	27.5	64
Manganese	---	---	---	40.2	24.7 - 25.4	9.5 - 35.8	4.1	---	7.0	20
Zinc	244.5	190.44	234	482.8	456.1 - 667.7	156.4 - 365.4	76	68	107.5	230

*Weight basis of reported concentrations not specified

[a] McDermott et al. concentrations reported in Table 1 were converted from ug/kg (ppb) to ug/g (ppm)

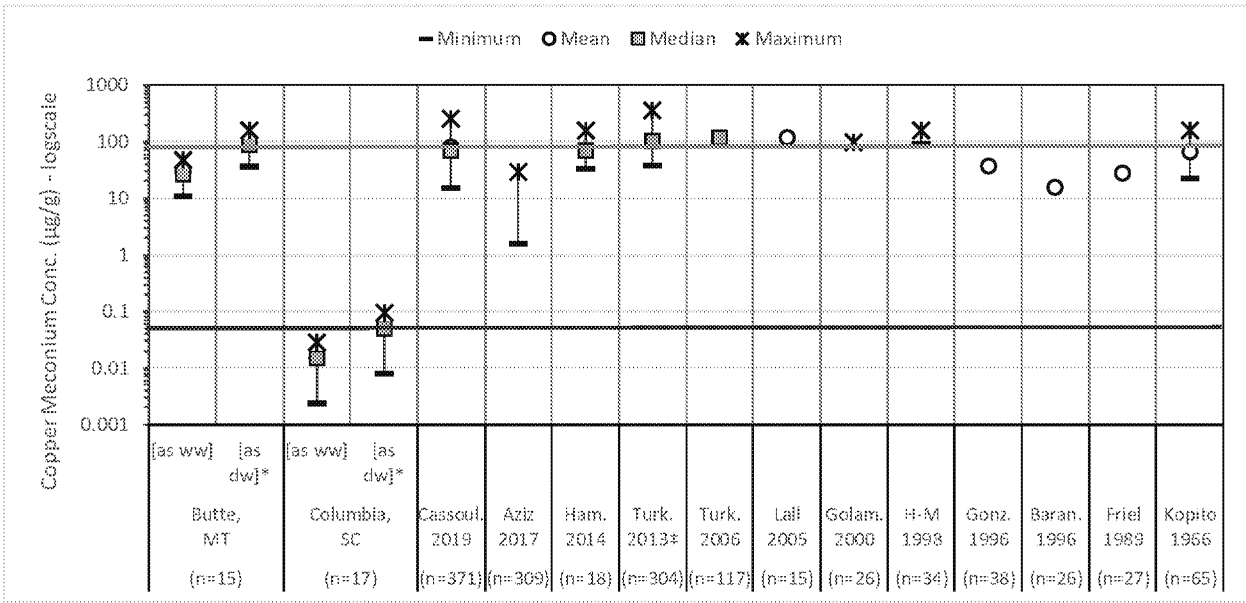
[b] McDermott et al. concentrations adjusted from wet weight to dry weight assuming a moisture content of 70% [dw = ww / (1 - 0.7)]

[c] Results reported in terms of infant body weight; adjusted based on the median body weight (2.070 kg).
Concentrations also adjusted to reflect corrected units based on personal communication from G. Turker to C. Partridge in January 2, 2020 email.

[d] Results reported in terms of total metal (expressed as concentration assuming the mean reported mass of stool 8.9 g)

FIGURE 1. COMPARISON OF MECONIUM METAL CONCENTRATIONS

Panel A: Copper



Panel B: Manganese

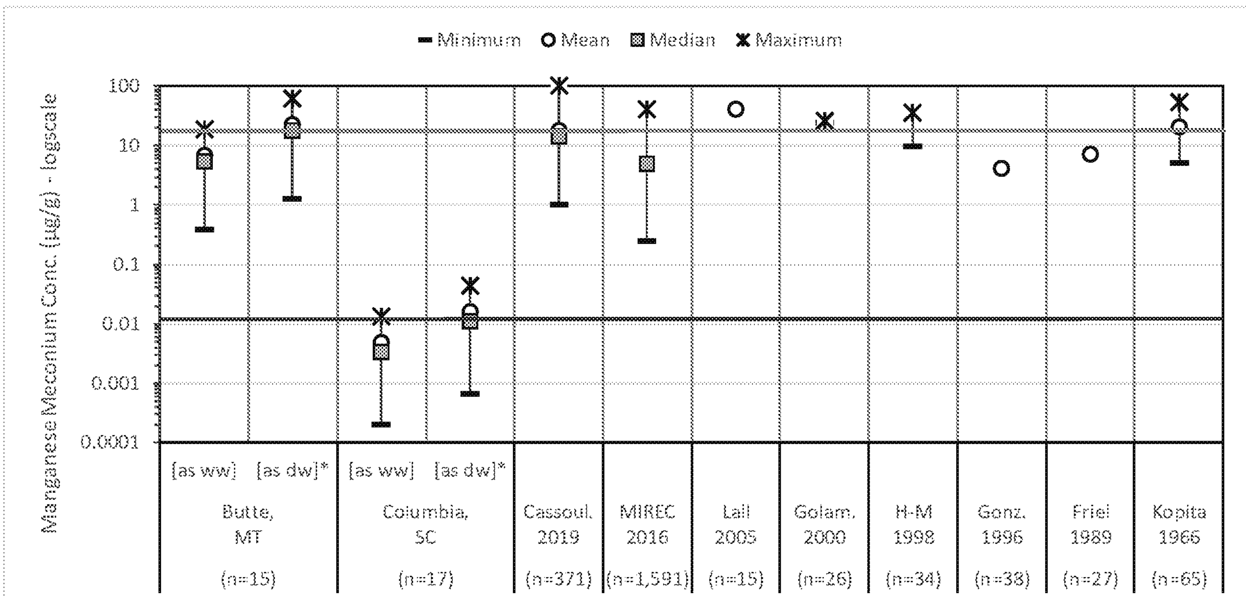
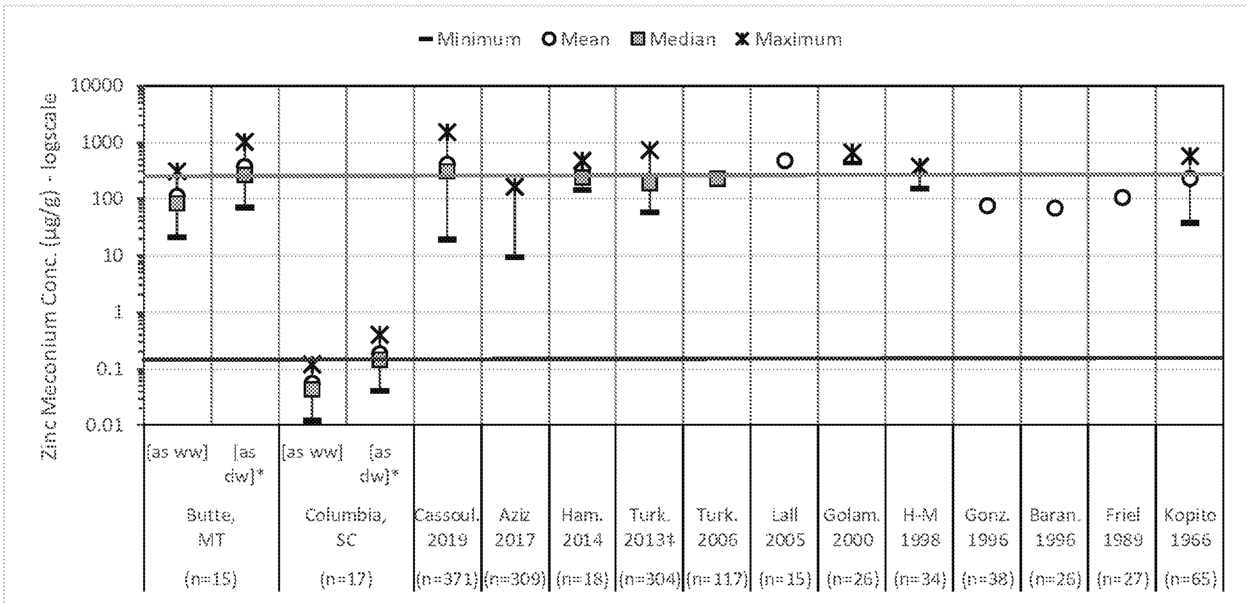


FIGURE 1. COMPARISON OF MECONIUM METAL CONCENTRATIONS [continued]

Panel C: Zinc



*McDermott concentrations adjusted from wet weight to dry weight assuming a moisture content of 70% [dw = ww / (1 - 0.7)]
‡Concentrations adjusted to reflect corrected units based on personal communication from G. Turker to C. Partridge in January 2, 2020 email.
All other values are as reported in the original citation; no adjustments for wet/dry weight have been made.
Green Line-mean dry weight (converted) Butte
Red Line-mean dry weight (converted) South Carolina